IBUPROFEN-CONTAINING SOFT GELATIN CAPSULES

Technical Field of the Invention

The technical field of the invention relates to ibuprofen-containing soft gelatin capsules, pharmaceutical compositions of a substantially clear ibuprofen solution, and process for their manufacture.

Background of the Invention

The insolubility of solid drug forms in common media such as water poses a major challenge because of the resulting low bioavailability of the active ingredients. Liquid dosage forms, in contrast, generally have better bioavailability. Liquid compositions, and especially concentrated liquid pharmaceutical compositions, offer many advantages over solid compositions. Liquids are easy to swallow and provide an excellent vehicle for the uniform delivery of pharmaceutical actives. Liquids also provide a rapid onset of pharmacological action, since the composition does not first have to disintegrate and dissolve in the gastrointestinal tract. Concentrated liquid compositions are ideally suited for encapsulation within a soft gelatin shell to provide a portable and easy-to-swallow soft, flexible capsule. Encapsulation also permits the accurate and uniform delivery of a unit dose of a pharmaceutical active ingredient, an advantage which becomes especially important when relatively small amounts of the active ingredient are to be delivered.

Additionally, soft gelatin capsules are aesthetically appealing, especially when filled with a transparent liquid, and can be manufactured in a wide variety of sizes, shapes, and colors. Furthermore, since the dosage form is generally swallowed, it is unnecessary to flavor or otherwise mask any unpleasant taste of the active pharmaceutical ingredients. Finally, unlike tablets, soft gelatin capsules do not chip or powder.

A particularly good bioavailability of the pharmacologically active substance is attained if the active substance is successfully dissolved in a suitable solvent and the encapsulated solution is administered to the patient. Solutions also provide the best liquid form to obtain optimal "content uniformity" in softgel fill. In addition, a solution provides a faster and more uniform absorption of a pharmaceutical agent than a suspension. Because of these distinct technical advantages, solutions generally are preferred over suspensions or other dispersions in some circumstances.

However, despite these advantages of liquid compositions, it is not always possible to prepare a liquid composition of the desired pharmaceutical active ingredient. Many pharmaceutical active ingredients are poorly soluble and therefore require relatively large volumes of solvent for dissolution. Also, the choice of solvents available for use in liquid compositions is limited by safety, compatibility, stability, and economic concerns. Furthermore, the use of large volumes of solvents for solubilizing pharmaceutical actives is undesirable because the resulting solutions would be so dilute as to require impractically large dosages for delivering a therapeutically effective amount of the active ingredient. In such situations, it would be difficult, if not impossible, to encapsulate such large volumes into only one or two gelatin capsules and yet have them be of a reasonable size for easy swallowing.

One approach to overcoming these solubility problems has been to incorporate water, water-miscible co-solvents, and surfactants into the compositions. U.S. Patent No. 4,794,117 discloses the solubilization of hydrophobic pharmaceuticals in aqueous solutions of polyethylene glycol at controlled pH; U.S. Patent No. 4,690,823 discloses the solubilization of ibuprofen in a mixture of polyethylene glycol and a surfactant.

U.S. Patent No. 5,484,606 describes the process for reducing the precipitation of difficult-to-solubilize pharmaceutical actives. The process uses propylene glycol to solubilize these actives along with polyethylene glycol and polyvinylpyrrolidine. U.S. Patent No. 5,071,643 discloses a solvent system that is characterized as enhancing the solubility of pharmaceuticals for encapsulation. The system involves the use of gelling agents such as sodium stearate, sodium palmitate and calcium acetate to improve solubility of pharmaceutical ingredients into polyethylene glycol.

U.S. Patent No. 6,287,594 discloses oral liquid compositions which are characterized as having improved bioavailability. The patent describes these compositions as being designed to provide drugs with minimal gastric irritability. The ratio of active drug to polymer based dispersing agent is from about 1:1 to 1:50 w/w. The resulting solution was found to be hazy.

U.S. Patent No. 6,387,400 discloses a process for improving concentration of a pharmaceutically active ingredient relative to fill composition. The process includes a two step process. In step one, a suspension of part of a drug is made in polyethylene glycol

with a molecular weight of 200 daltons to 100,000 daltons and solubilizing it subsequently with hydroxide ion. In step two, the remaining drug is added and the resulting suspension is solubilized by adding the remaining part of hydroxide ion. The ratio of drug to fill material by weight is 1:2 and/or 5:9.

U.S. Patent No. 5,919,481 discloses fill material for soft gelatin capsule that is translucent and semisolid in nature. The fill material uses cellulose ether and polyalkylene glycol with an average molecular weight of about 600 or less.

U.S. Patent No. 5,141,961 discloses a process for solubilizing difficult-to-solublize pharmaceutical actives. This process uses polyethylene glycol, polyvinylpyrrolidine and monohydric alcohols. The ratio of polyethylene glycol to polyvinylpyrrolidine is about 2.5 to 1. The process does not involve the use of heat, solvents or surfactants.

Thus, the problem of finding an appropriate solvent system for a soft gelatin capsule fill still exists for ibuprofen. It has been difficult to achieve a soft gelatin capsule of small enough size to be acceptable to patients, i.e., small enough to swallow while still including in that capsule a sufficient amount of ibuprofen in a clear and stable solution to provide an effective unit dose.

Summary of the Invention

In one general aspect there is provided a clear ibuprofen composition that includes from about 15% to about 40% w/w of ibuprofen, from about 15% to about 25% w/w of polyethylene glycol, from about 20% to about 50% w/w of a surfactant, from about 1% to about 5% w/w of an alkalizing agent, and from about 5% to about 10% w/w of water.

Embodiments of the composition may include one or more of the following features. For example, the ibuprofen may make up about 15% to about 30% w/w of the composition. The composition may be filled into soft gelatin capsules.

The polyethylene glycol may have an average molecular weight of about 300 to about 1000 and more particularly a molecular weight of about 400.

The surfactant may be a non-ionic hydrophilic surfactant. The non-ionic hydrophilic surfactant may be one or more of polyoxyethylene alkylethers, polyethylene glycol fatty acids esters, polyethylene glycol glycerol fatty acid esters, polyoxyethylene sorbitan fatty acid esters, polyoxyethylene-polyoxypropylene block copolymers,

polyglyceryl fatty acid esters, polyoxyethylene glycerides, polyoxyethylene vegetable oils, and polyoxyethylene hydrogenated vegetable oils. In particular, the surfactant may be polyoxyethylene sorbitan fatty acid ester.

The alkalizing agent may be one or more of amino acids, amino acid esters, diisopropylethylamine, ethanolamine, ethylenediamine, triethanolamine, meglumine, trimethylamine, triethylamine, triisopropanolamine and salts of pharmaceutically acceptable acids.

The salts of pharmaceutically acceptable acids may be one or more of ammonium hydroxide, potassium hydroxide, sodium hydroxide, sodium hydrogen carbonate, aluminum hydroxide, calcium carbonate, potassium carbonate, magnesium hydroxide, magnesium aluminum silicate, synthetic aluminum silicate, magnesium aluminum hydroxide and calcium silicate. In particular, the salt may be potassium carbonate.

The composition may further include one or more active ingredients. The additional active ingredients may be one or more of glucosamine, pseudoephedrine, codeine, paracetamol, econazole, hydrocodone, COX-2 inhibitors, alprazolam, dextromethorphan and chlorpheniramine.

In another general aspect there is provided a process of preparing a clear ibuprofen composition. The process may include the steps of (a) dissolving one or more alkalizing agents in water to form a solution, (b) dispersing ibuprofen in polyethylene glycol to form a dispersion, (c) blending the solution of step (a) with the dispersion of step (b) with continuous stirring to form a dispersion, (d) optionally heating the dispersion of step (c), and (e) adding one or more surfactants to the dispersion of step (d) and mixing to obtain a clear solution.

Embodiments of the process may include one or more of the following features. For example, the ibuprofen may make up from about 15% to about 30% w/w of the composition.

The polyethylene glycol may have an average molecular weight ranging from about 300 to about 1000. In particular, the polyethylene glycol may have a molecular weight of about 400.

The surfactant may be a non-ionic hydrophilic surfactant. The non-ionic hydrophilic surfactant may be one or more of polyoxyethylene alkylethers, polyethylene glycol fatty acids esters, polyethylene glycol glycerol fatty acid esters, polyoxyethylene sorbitan fatty acid esters, polyoxyethylene-polyoxypropylene block copolymers, polyglyceryl fatty acid esters, polyoxyethylene glycerides, polyoxyethylene vegetable oils, and polyoxyethylene hydrogenated vegetable oils. In particular, the surfactant may be polyoxyethylene sorbitan fatty acid ester.

The alkalizing agent may be one or more of amino acids, amino acid esters, diisopropylethylamine, ethanolamine, ethylenediamine, triethanolamine, meglumine, trimethylamine, triethylamine, triisopropanolamine and salts of pharmaceutically acceptable acids.

The salts of pharmaceutically acceptable acids may be one or more of ammonium hydroxide, potassium hydroxide, sodium hydroxide, sodium hydrogen carbonate, aluminum hydroxide, calcium carbonate, potassium carbonate, magnesium hydroxide, magnesium aluminum silicate, synthetic aluminum silicate, magnesium aluminum hydroxide and calcium silicate.

The process may further include adding one or more active ingredients. The active ingredients added may be one or more of glucosamine, pseudoephedrine, codeine, paracetamol, econazole, hydrocodone, COX-2 inhibitors, alprazolam, dextromethorphan and chlorpheniramine.

In another general aspect there is provided a method of relieving one or more of pain, tenderness, inflammation and stiffness caused by one or more of arthritis and gout and pains from one or more of the common cold, backache, and pain after surgery or dental work. The includes administering a clear ibuprofen composition that can include from about 15% to about 40% w/w of ibuprofen, from about 15% to about 25% w/w of polyethylene glycol, from about 20% to about 50% w/w of surfactant, from about 1% to about 5% w/w of alkalizing agent, and from about 5% to about 10% w/w of water.

The method may include one or more of the following or the features described above. For example, the composition may further include one or more of glucosamine, pseudoephedrine, codeine, paracetamol, econazole, hydrocodone, COX-2 inhibitors, alprazolam, dextromethorphan and chlorpheniramine.

The details of one or more embodiments of the inventions are set forth in the description below. Other features, objects and advantages of the inventions will be apparent from the description and claims.

Detailed Description of the Invention

Hydrophobic therapeutic agents, i.e., therapeutic compounds having poor solubility in aqueous solution, present problems in formulating such compounds for effective administration to patients. A well-designed formulation must be capable of presenting a therapeutically effective amount of the hydrophobic compound to the desired absorption site, in an absorbable form. Even this minimal functionality may be difficult to achieve when delivery of the hydrophobic therapeutic agent requires interaction with aqueous physiological environments, such as gastric fluids and intestinal fluids. Pharmaceutical compositions for delivery of such hydrophobic therapeutic agents must carry the hydrophobic compound through the aqueous environment while maintaining the hydrophobic compound in an absorbable form and avoiding the use of physiologically harmful solvents or excipients.

Soft gelatin capsules or softgels are predominantly used to contain liquids wherein the active ingredients are present in the dissolved or suspended state. Solutions also provide the best liquid form to obtain optimal "content uniformity" in softgel fill. In addition, a solution provides a faster and more uniform absorption of a pharmaceutical agent than a suspension. Because of these distinct technical advantages, solutions often are preferred over suspensions or other dispersions.

However, an appropriate solution of the pharmaceutical agent cannot always be achieved. Often, it is not possible to dissolve the pharmaceutical agent in a volume of solvent small enough to produce a softgel that is appropriate from the standpoint of economics and patient acceptance. Another constraint is the solvent itself. The solvent must have sufficient solvating power to dissolve a large amount of the pharmaceutical agent to produce a clear solution, and yet not hydrolyze, dissolve, or discolor the softgel capsule shell.

The present invention provides clear and stable solutions of ibuprofen and the process of preparing them.

The term 'clear solutions', as used herein, describes liquid pharmaceutical compositions that are transparent and free from turbidity or cloudiness or any other foreign particulate matter.

The clear and stable solutions of ibuprofen generally include:

a. from about 15% to about 40% w/w of ibuprofen,
b. from about 15% to about 25% w/w of polyethylene glycol,
c. from about 20% to about 50% w/w of surfactant,
d. from about 1% to about 10% w/w of alkalizing agent, and
e. from about 5% to about 10% w/w of water.

Polyethylene glycols generally are clear, viscous liquids or white solids, which are soluble in water and many organic solvents. The polyethylene glycols useful herein are those which are liquids at room temperature or have a melting point slightly there above. Preferred polyethylene glycols are those having a molecular weight range from about 300 to about 1000. More preferred are the polyethylene glycols having a molecular weight range from about 400 to about 1000. Moreover, mixtures of two or more polyethylene glycols of different average molecular weight range can also be employed in the present invention. It has been observed that for preparing highly concentrated liquid compositions, concentrations of about 40 to about 60% w/w of polyethylene glycol are generally employed. However, in the present invention we have prepared clear solutions by employing less than 25% w/w of polyethylene glycol. Particularly, the present invention employs from about 15% to about 25% w/w of polyethylene glycol.

The composition may include at least one surfactant. Suitable surfactants can be ionic hydrophilic surfactants or non-ionic hydrophilic surfactants. The surfactant can be any surfactant suitable for use in pharmaceutical compositions. Suitable hydrophilic surfactants may be anionic, cationic, zwitterionic or non-ionic; particularly non-ionic hydrophilic surfactants. Suitable non-ionic hydrophilic surfactants include one or more of polyoxyethylene alkylethers; polyethylene glycol fatty acids esters; polyethylene glycol glycerol fatty acid esters; polyoxyethylene sorbitan fatty acid esters; polyoxyethylene-polyoxypropylene block copolymers; polyglyceryl fatty acid esters; polyoxyethylene glycerides; polyoxyethylene vegetable oils; polyoxyethylene hydrogenated vegetable oils; reaction mixtures of polyols and at least one member selected front the group consisting of

fatty acids, glycerides, vegetable oil hydrogenated vegetable oils, and sterols; and mixtures thereof. In particular, polyoxyethylene sorbitan fatty acid esters are employed.

An alkalizing agent may also be added to the composition to assist in the dispersion of the ibuprofen during the formulation of the composition. Suitable alkalizing agents that are commonly used are amino acids, amino acid esters, diisopropylethylamine, ethanolamine, ethylenediamine, triethanolamine, meglumine, trimethylamine, triethylamine and triisopropanolamine. Also suitable are bases which are salts of a pharmaceutically acceptable acid, such as acetic acid, acrylic acid, adipic acid, alginic acid, alkanesulfonic acid, amino acids, ascorbic acid, benzoic acid, boric acid, butyric acid, carbonic acid, citric acid, fatty acids, formic acid, fumaric acid, gluconic acid, hydroquinosulfonic acid, isoascorbic acid, lactic acid, maleic acid, oxalic acid, para-bromophenylsulfonic acid, propionic acid, p-toluenesulfonic acid, salicylic acid, stearic acid, succinic acid, tannic acid, tartaric acid, thioglycolic acid, toluenesulfonic acid, uric acid, and the like. Salts of polyprotic acids, such as sodium phosphate, disodium hydrogen phosphate, and sodium dihydrogen phosphate can also be used. When the base is a salt, the cation can be any convenient and pharmaceutically acceptable cation, such as ammonium, alkali metals, alkaline earth metals, and the like. Preferred cations include sodium, potassium, lithium, magnesium, calcium and ammonium. The basic amino acids can be, for example, L-arginine, L-histidine, prolamine, or mixtures thereof. The salts of pharmaceutically acceptable acids may be ammonium hydroxide, potassium hydroxide, sodium hydroxide, sodium hydrogen carbonate, aluminum hydroxide, calcium carbonate, potassium carbonate, magnesium hydroxide, magnesium aluminum silicate, synthetic aluminum silicate, magnesium aluminum hydroxide, calcium silicate or mixtures thereof. In particular, the alkalizing agent is potassium carbonate.

The present solvent system in its simplest form includes polyethylene glycol, alkalizing agent and water. Without being limited by theory, the polyethylene glycol acts to dissolve the free form of the acidic agent; the alkalizing agent is present in a sufficient quantity to only partially form the alkali salt of the acidic pharmaceutical agent; and the small amount of water present acts to form a solvation sphere around the acid salt permitting it to go into solution in the polyethylene glycol. Water may be present in amounts ranging from about 5% to about 10% by weight of the solution.

A process of preparing the pharmaceutical composition includes the steps of:

a. dissolving alkalizing agent in water,

b. dispersing ibuprofen in polyethylene glycol,

c. blending the solution of step (a) with the dispersion of step (b) with continuous stirring, and

d. adding surfactant to the dispersion of step (c) and mixing to obtain a clear solution.

Compositions of the invention are useful in relieving the pain, tenderness, inflammation (swelling) and stiffness caused by arthritis and gout. It may also be used to reduce fever and to relieve particular and general pain, such as headaches, muscle aches, menstrual pain, aches and pains from the common cold, backache, and pain after surgery or dental work.

The pharmaceutical composition may further include one or more of glucosamine, pseudoephedrine, codeine, paracetamol, econazole, hydrocodone, COX-2 inhibitors, alprazolam, dextromethorphan and chlorpheniramine. The ibuprofen and the one or more active ingredients may be combined in a single pharmaceutical composition, such as a sft gelatin capsule or softgel.

The following examples illustrate various aspects of the present inventions. These examples are for illustration only and do not limit the scope of the inventions.

EXAMPLES 1-3

S. No.	Ingredients	mg / capsule		
		1	2	3
1.	Ibuprofen	200.0	200.0	200.0
2.	Polyethylene glycol	178.0	163.0	142.0
3.	Polyoxyethylene sorbitan fatty acid ester	280.0	290.0	311.0
4.	Potassium carbonate	27.0	27.0	27.0
5.	Purified water	40.0	40.0	40.0
	Total	725	720	720

Process:

a. Potassium carbonate was dissolved in purified water.

b. Ibuprofen was separately dispersed in polyethylene glycol.

c. The solution of step a was blended with the dispersion of step b under constant stirring to form a dispersion.

d. To the dispersion of step c, polyoxyethylene sorbitan fatty acid ester was added and stirred until a clear solution was formed.

e. The clear solution of step d was filled in soft gelatin capsules.

EXAMPLE 4

S. No.	Ingredients	mg / capsule
6.	Ibuprofen	200.0
7.	Polyethylene glycol	178.0
8.	Polyoxyethylene sorbitan fatty acid ester	280.0
9.	Meglumine	27.0
10.	Purified water	40.0
	Total	725

Process: Similar to that of Examples 1-3, forms a clear solution.

EXAMPLE 5

S. No.	Ingredients	mg / capsule
11.	Ibuprofen	200.0
12.	Polyethylene glycol	178.0
13.	Polyoxyethylene sorbitan fatty acid ester	280.0
14.	Calcium silicate	27.0
15.	Purified water	40.0
	Total	725

Process: Similar to that of Examples 1-3, forms a clear solution.

EXAMPLE 6

S. No.	Ingredients	mg / capsule
16.	Ibuprofen USP	200.0
17.	Povidone USP (PVP K30)	30.0
18.	Polysorbate 80 USNF	90.0
19.	Meglumine USP	27.0
20.	Polyethylene glycol 600 USNF	363.0.0
21.	Purified water	40.0
	Total	750.0

While several particular forms of the inventions have been described, it will be apparent that various modifications and combinations of the inventions detailed in the text can be made without departing from the spirit and scope of the inventions. Accordingly the inventions are not limited, except as by the appended claims.